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PERSPECTIVE

Considering the Effects of Microbiome and Diet on SARS-CoV-2 Infection: Nanotechnology Roles

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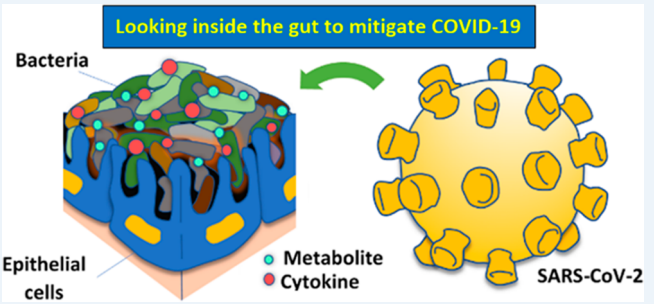
ABSTRACT: **The impact of dietary patterns and the commensal microbiome on susceptibility to and severity of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has been largely ignored to date. In this Perspective, we present a rationale for an urgent need to investigate this possible impact and therapeutic options for COVID-19 based on dietary and microbiome modifications. The mitigating role of nanotechnology with relation to the impact of SARS-CoV-2 virus is highlighted.**



Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes coronavirus disease 2019 (COVID-19). Since its first detection in December 2019, it has affected millions of people worldwide, carrying a mortality rate much higher than any common flu. While there is an urgent need for its effective treatment based on antivirals and vaccines, it is imperative to explore any other effective intervention strategies that may reduce the mortality and morbidity rates of this disease.

It may be possible to look in the gut for a solution to or mitigation of SARS-CoV-2 infection. The ecosystem of the gut and commensal microbiota can both regulate and be regulated by invading viruses, facilitating either stimulatory or suppressive effects.[1] Therefore, it is plausible to consider whether the gut and SARS-CoV-2 interaction may play significant roles in the intensity of the infection and its clinical outcomes.

Is it possible to look in the gut for a solution to SARS-CoV-2 infection?

The integrity of the gut microbiome (the collective genomes of the diverse microbiota that reside in the gastrointestinal tracts of humans) could conceivably be disturbed by SARS-CoV-2, causing gut dysbiosis in the host (Figure 1), as with other infectious diseases. There are signs that may connect gut functionality and microbiome responses to SARS-CoV-2. For instance, the incubation period for SARS-CoV-2 is typically 5–6 days, whereas the average incubation period for influenza is 2 days,[2] and diarrhea can be a presenting feature in SARS-CoV-2 patients.[3] New research indicates that SARS-CoV-2 may be spread by fecal–oral transmission.[4] The highest SARS-CoV-2 mortality and morbidity is in the elderly and in those with underlying health problems that are associated with inflammation and other disorders, such as diabetes.[5] Interestingly, these cohorts tend to have less diverse gut microbiomes.[6]

Links between the gut microbiome and age-related health decline have been consistently shown.[7] Aging is associated with significant shifts in microbiome diversity and pro-inflammatory states. The elderly microbiome generally shows a shift away from Firmicutes, which dominates in younger adults, toward genera such as *Alistipes* and *Parabacteroides*.[8] A strong interindividual variability has been characterized in the elderly gut microbiome, with fluctuations featuring *Faecalibacterium* and *Ruminococcus* as well as certain *Clostridium* clusters, especially IV and XIVa. These may explain, in part, the different impacts of viral infections in elderly individuals.

There are also specific trends in microbiome shifts that are seen in asthmatic and diabetic patients. Interestingly, asthma

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ACS Nano XXXX, XXX, XXX–XXX

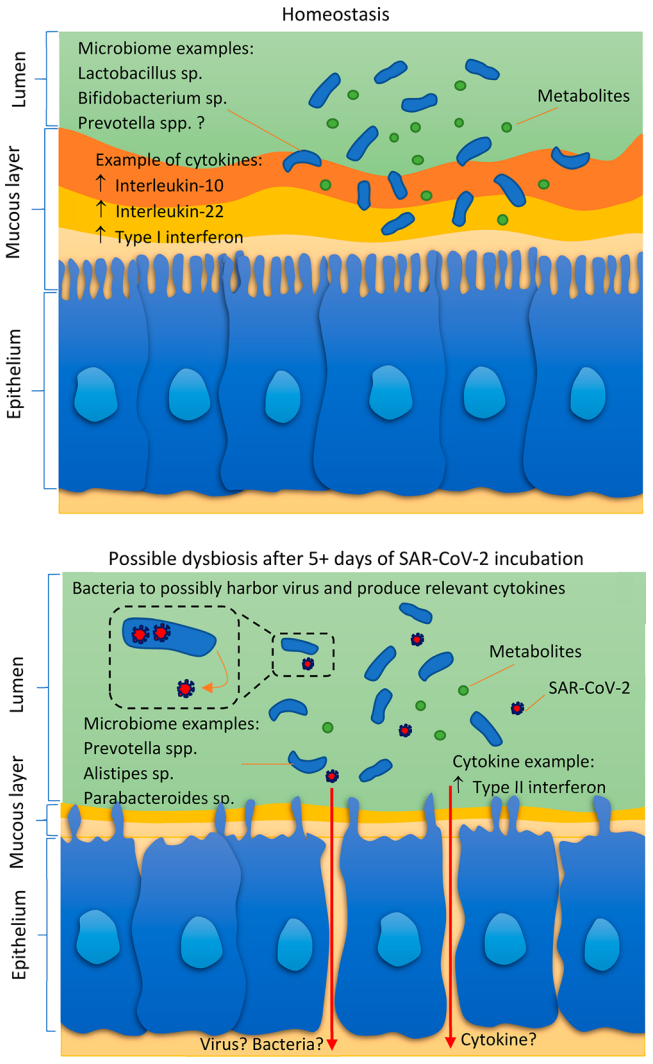

Figure 1. Homeostasis *versus* possible mechanisms of dysbiosis by SAR-CoV-2 virus infection.

appears to be *underrepresented* among comorbidities for critically ill patients infected with SARS-CoV-2.[9] In severe asthma, asthma control and sputum neutrophilia are associated with Proteobacteria phylum relevant to pathogens such as *Escherichia*, *Salmonella*, *Vibrio*, and *Helicobacter*.[10] Additionally, in chronic obstructive airways disease, the phylum *Bacteroidetes* (*e.g.*, *Prevotella*) is decreased.[10] In contrast, the numbers of the H_2-producing *Prevotellaceae* (*e.g.*, *Prevotella*) were highly enriched in obese individuals prone to type II diabetes.[11] Additionally, an abundance of *Bifidobacteria* (which can produce butyrate) in type II diabetes patients has been shown to improve glucose tolerance.[12] In relation to this issue, attention should be given to interesting, but limited, reports regarding the abundance of *Prevotella* in sequencing data sets of COVID-19 patients.[13−15]

An essential step for understanding the effect of the gut on SARS-CoV-2 is identifying the main gut microbiome species interacting with this virus. In this regard, the possibility that SARS-CoV-2 can interact with one or many of the 1500 species of microbiota in the gut makes the matter complicated. As such, without any human trials, it is impossible to refer to any specific species that influences SARS-CoV-2 pathogenesis. However, it is possible to consider the hypothesis of SARS-CoV-2 gut interaction based on past evidence. Many different direct or indirect microbiome pathways could contribute to SARS-CoV-2-gut interactions. Considering the pulmonary inflammation seen in SARS-CoV-2 patients in the second week of infection, both direct or indirect pathways can be taken into consideration. Direct suppression or promotion of viral infection by the microbiome can occur *via* various mechanisms, such as genetic recombination, alteration of virion stability, driving the proliferation of cells, simulating attachment to permissive cells, and contributing to viral replication suppression; promotion of viral infection may occur by inducing systems' immunoregulatory and perturbing local immune responses.[1]

> Many different direct or indirect microbiome pathways could contribute to SARS-CoV-2-gut interactions.

Although reports on direct and indirect viral bacterial promotion for influenza viruses are rare, examples of observed suppression are manifold. *Lactobacillus* species, as a result of carbohydrate fermentation, can produce lactic acid, and the consequent pH changes inactivate different viruses.[1] The integrity of epithelial cells in the gut is important, as they produce antiviral compounds that are hostile to viruses. The colonic epithelial cells' functionality relies largely on the luminal presence of butyrate as an energy source, and the main butyrate-producing bacteria in the gut belongs to the phylum Firmicutes.

One hypothesis regarding microbiome interactions with SARS-CoV-2 is relevant to the microbiomes' impacts on cytokines. Cytokines are small proteins that coordinate the body's response against infection and inflammation. For example, type II interferon (interferon-γ) classically play important roles in antiviral responses.[16] More importantly, microbial metabolic processes in the gut strongly impact the production of cytokines. Microbiota can increase chronic phase proteins and interferon signaling in lung cells to protect against influenza infection. However, as in the case of SARS-CoV-2, the body's response to infection can go into overdrive. In some patients, the immune response against SARS-CoV-2 results in excessive levels of cytokines release, leading to hyper-inflammation and, clinically, to severe acute respiratory distress syndrome (SARDS) and multi-organ failure. So far, a cytokine profile associated with SARS-CoV-2 disease severity has been characterized by increased interferon-γ inducible protein 10 as well as many other cytokines.[2] Therefore, the elucidation of host cytokine molecular pathways and microbiota components[17] as well as bacterial reactions in association with cytokine responses may provide novel microbiome-based therapeutic approaches to SARS-CoV-2 infection.

As of yet, no study has been reported to identify the microbiota species that interact with SARS-CoV-2. Considering the presented discussion, nutritional and dietary strategies directed at restoring the well-known beneficial microbiota, which can possibly suppress viral infection in the elderly and those with underlying health problems, may be an effective strategy to mitigate the harmful effects of this virus.

One approach, as a whole and to be undertaken prior to any viral infection, could include strengthening the intestinal barrier against pathogens, increasing intestinal motility, and reducing an underlying pro-inflammatory state by adopting a

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ACS Nano XXXX, XXX, XXX−XXX

Nutritional and dietary strategies directed at restoring the well-known beneficial microbiota, which can possibly suppress viral infection in the elderly and those with underlying health problems, may be an effective strategy to mitigate the harmful effects of this virus.

more varied diet with a moderate increase in high-fiber and plant-based foods. Of particular relevance is the enhancement of intestinal butyrate production through the promotion of microbial interactions by dietary changes. This change enhances gut epithelial cell health. In this regard, the shifts around the core microbiome including *Bifidobacteria*, *Lactobacilli*, and *Prevotella* are critical. Universally, *Bifidobacteria* and *Lactobacilli* are considered beneficial species regarding butyrate production, while the description of the functionality of *Prevotella* remains controversial (Figure 1).

Importantly, *Prevotella* has been abundantly seen in the clinical samples of SARS-CoV-2 infected patients,[11−13] and the interpretation of its role is challenging and unclear. It is still not known whether *Prevoltella* becomes abundant as a consequence of viral modulation or, conversely, is modulating SARS-CoV-2. It is unclear if this abundance of *Prevotella* is due to long-standing dietary patterns or originates from modulation of the microbiome after the invasion of the virus. Depending on whether *Prevotella*'s presence should be amplified or suppressed, the appropriate therapeutic action could be chosen. Past studies suggest that high-fat diets increase the abundance of *Prevotella*, whereas plant-based diets and fermented foods result in the opposite.[18]

As general advice, frequent snacking between meals may cause dysbiosis and so should be kept to a minimum and only constitute fruit and vegetables, if required. The impact of probiotics should also be investigated. Probiotics may help by interacting with the intestinal microbiota and modulating the immune system directly or through modification of the gut microbiota. The most commonly regarded beneficial probiotics in foods are *Bifidobacteria* and *Lactobacilli* species. In this regard, while still not having any full knowledge about beneficial or harmful strains, diets adhering to modest qualities of naturally fermented food are likely to be effective as preventative measures against SARS-CoV-2 and are of no risk for damaging the integrity of the gut and dysbiosis (Figure 1). Without having knowledge about the best acting microbiota strains in response to SARS-CoV-2, following a healthy, moderate calorie, moderately higher fiber, and more diverse diet is a logical approach to mitigate the severity of this viral infection as a plausible preventive action. An essential investigation into the microbiome of COVID-19 patients will be able to reveal the association of this disease to clinical outcomes of such preventative strategies.

VISION FOR FUTURE RESEARCH APPROACHES

Associations between dietary and microbiome effects and susceptibility to infection and severity of illness should be investigated with different methodologies. The overarching strategy should involve large, adequately powered international studies that recruit COVID-19 patients and controls to collect clinical data, detailed dietary assessments, host genetics, immune phenotyping, and multi-site multiomic microbiome markers. The international approach would enable the inclusion of populations from different regions with different backgrounds, various dietary patterns, and environmental exposures. This comprehensive and collaborative approach is essential for unravelling the determinants of clinical outcomes of this infection and for designing targeted therapeutic and preventative measures. The moderating effects of high fiber (especially the choice of the high-fiber food type), freshly fermented, and diverse foods should also be examined as preventative and mitigating measures.

Without having knowledge about the best acting microbiota strains in response to SARS-CoV-2, following a healthy, moderate calorie, moderately higher fiber, and more diverse diet is a logical approach to mitigate the severity of this viral infection for now.

NANOTECHNOLOGY-ENABLED ACTIONS

In the light of the presented discussion, nanotechnology may play a critical role for rapid diagnosis, monitoring, and the design of effective therapeutic actions for COVID-19 with relevance to the gut modulation by SAR-CoV-2. Non-invasive breath tests, with arrays of nanomaterials, can identify the presence of volatile organic compounds with the signatures of modulated microbiota (abundance of *Prevotella*, for example) and, hence, recognize the presence of SAR-CoV-2 for quick diagnosis and monitoring.[19,20] Ingestible sensors can be designed for the detection of inflammatory proteins associated with COVID-19.[21] If the therapeutic strategy relies on the elimination of a specific bacterial strain in the gut, broad spectrum antibiotics would *not* work, as they also eliminate beneficial bacteria and consequently weaken the gut barrier. Nanotechnology can efficiently be implemented in designing intelligent drugs or functional foods, with the possibility of localized delivery in the gut,[22] and also in designing intelligent functional foods.[23] These drugs and foods should target problematic bacterial strains in the gastrointestinal tract and enhance its health by improving gut barriers against pathogens and inflammatory reagents and by providing the base for creating disruptive remedies based on microbiome engineering.[19] Nanoscale-enabled tools will likely enable us to observe, to navigate, and to act through the complicated ecosystem of the gut to help in finding either a cure or mitigating procedures for COVID-19 and keeping SAR-CoV-2 under control.

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Notes

The authors declare no competing financial interest.

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ACS Nano XXXX, XXX, XXX−XXX